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Editor's Corner

How Shall I Eat Thee?

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"All the cell's a stage, and all the cytoplasm in it merely a substrate for autophagy."

From As You Eat It in Shakespeare for the Cell Biologist

If you work in the field of autophagy we do not really need to tell you that this research area has grown tremendously. Along with that growth has developed a need for some unification of the nomenclature. In 2003, researchers working with the yeast model system proposed the use of the acronym *ATG* to denote AuTophagy-related genes,¹ and this designation has also been adopted for most of the genes involved in autophagy in higher eukaryotes. Similarly, a common nomenclature for isoforms of lysosome associated protein type 2 (LAMP-2) was recently proposed, hopefully reducing some of the confusion resulting from the use of multiple names.² At this time we thought it worthwhile to consider the terms being used to describe different types of lysosomal or vacuolar degradative pathways. Many names are being introduced, and this is reasonable to the extent that these various processes have distinct features; each unique process needs a specific name to avoid confusion, and to eliminate the need for a lengthy description. It would be helpful, however, if the community agreed on their use. Finally, the addition or use of a name that implies a unique process must be backed up by data that justify the nomenclature. Thus, researchers should verify that a process is specific before using a name that implies specificity. For example, to demonstrate selectivity in organelle degradation it is incumbent upon the researcher to show that the organelle in question, and not other organelles, is sequestered and/or degraded with kinetics that distinguish it from a bulk, nonspecific process.

There are many types of autophagy. To our knowledge, the term "autophagy" (from the Greek "auto" for "self" and "phagein" meaning "to eat") was first used in a 1963 review article by Christian de Duve.³ The first reference we have found in a research paper is in regard to a possible role of autophagy in lung cancer;⁴ however, as this work was published in an Italian journal, we are not able to comment on this in any authoritative manner. The following year, de Duve published a highly referenced review,⁵ and by this time the authors unquestionably refer to the process of macroautophagy, although the actual term was introduced later.⁶ Perhaps the most distinguishing feature of macroautophagy for the purposes of this discussion is that it involves the generally nonspecific (see ref. 7 for an exception) sequestration of cytoplasm within a non-lysosomal/vacuolar compartment, usually delimited by a double or multiple membrane; this compartment is typically referred to as an autophagosome.

Another long-standing term that has not seen tremendous usage of late, but that is experiencing renewed interest, is "crinophagy" that is derived from the Greek "crin" meaning, "to secrete". As far as we can tell this name also derives from de Duve.⁸ "Crinophagy" was originally used to describe the direct fusion of secretory vesicles with lysosomes (e.g., see refs. 9–11), resulting in the formation of a "crinosome."¹² This topic has attracted recent attention because of possible connections with diabetes, as crinophagy appears to be used for the regulated degradation of vesicle-stored insulin.¹³ It is not known whether insulin degradation incorporates any aspects of macroautophagy, but that possibility has not been ruled out. We suggest that we retain the use of the term "crinophagy" as it was originally described; if it turns out that the degradation of insulin does involve a macroautophagic process, we think we will need to introduce another name. We note that "insulinophagy" should be avoided because the target of degradation would presumably be the vesicles that contain insulin rather than the hormone itself. One possibility would be "secrephagy" to note that the target is secretory vesicles, or alternatively "macrocrinophagy."

There is probably no controversy about the use or meaning of the name "chaperone-mediated autophagy" (CMA),¹⁴ which is a process involving the direct translocation of

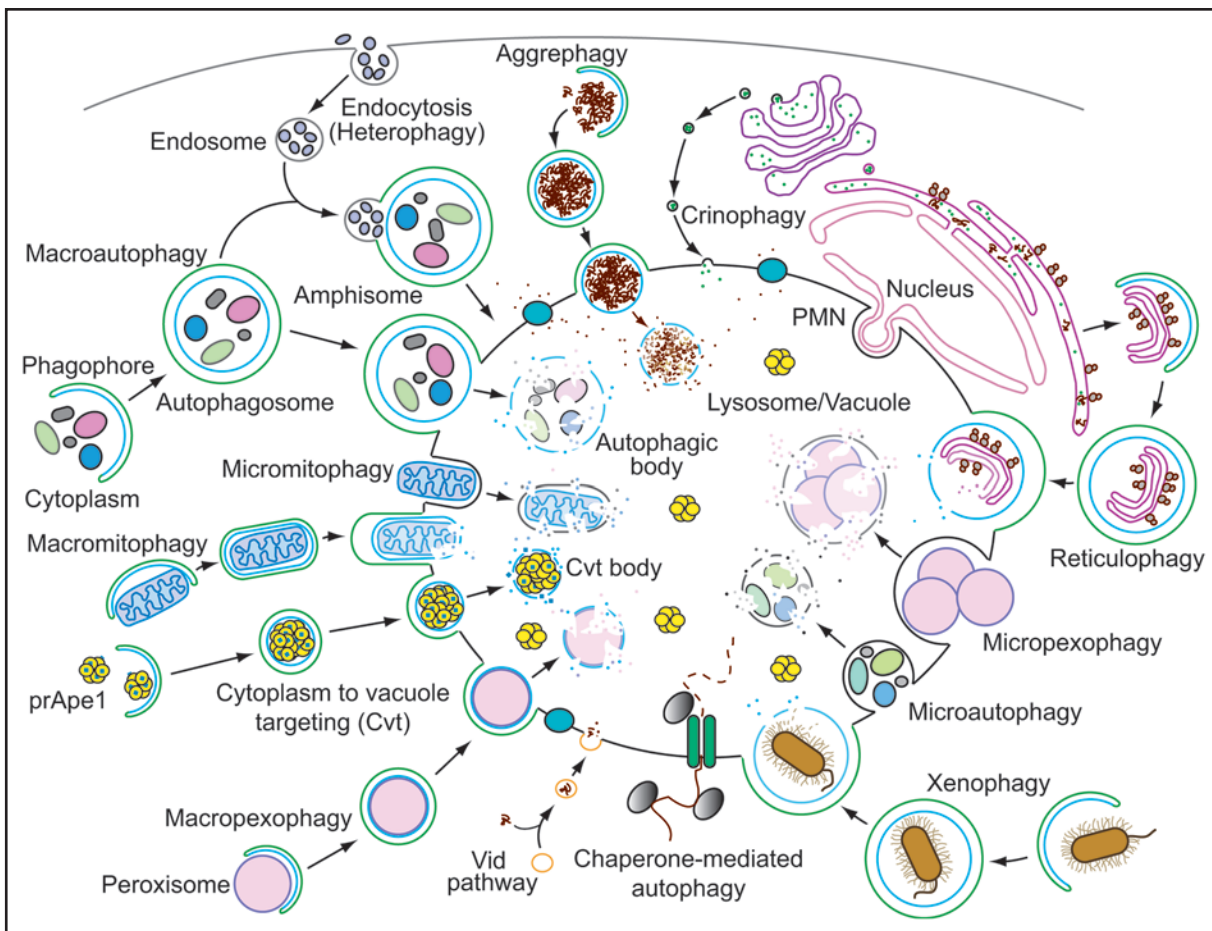


Figure 1. A schematic drawing of degradative pathways involving the lysosomal/vacuolar systems; the model depicts aspects of yeasts and higher eukaryotes. Compartments and proteins are not drawn to scale. The amphisome is a convergence point between endocytosis and autophagy. PMN, piecemeal microautophagy of the nucleus; Vid, vacuole import and degradation. See text for additional information.

proteins into the lysosome in an hsc70-mediated manner. Similarly, the term “microautophagy” does not need anything in the way of further definition at this time, although that is largely because we do not know very much about it. The “vacuole import and degradation” (Vid) pathway is a type of degradative process used for the selective turnover of fructose-1,6-bisphosphatase.¹⁵ There is no controversy about the name of this process, and the only confusion stems from the apparent fact that fructose-1,6-bisphosphatase is degraded by an autophagy-like pathway as well as via the proteasome, depending on the specific growth conditions.¹⁶ Portions of the nucleus can be degraded through “piecemeal microautophagy of the nucleus” (PMN),¹⁷ whereas the “cytoplasm to vacuole targeting” (Cvt) pathway is a biosynthetic route used for the delivery of certain resident vacuolar hydrolases in yeasts.¹⁸ These latter names are generally accepted. Accordingly, we will focus the remainder of the discussion on different types of autophagic sequestration that warrant further consideration, as well as briefly considering the history behind some of the corresponding names.

A newer term that was proposed for an autophagy-like process that is now generally accepted by researchers is “pexophagy.”¹⁹ Pexophagy, or selective peroxisome degradation through an autophagy-related mechanism, can occur through either micropexophagy or macropexophagy.²⁰ There is one primary point of contention regarding the use of the term “pexophagy.” All researchers studying this process probably agree that when cells are shifted from conditions

in which peroxisomal enzymes are needed for metabolism, such as during growth on oleic acid or methanol, to a condition in which these enzymes are no longer needed, such as growth on glucose, the process of degradation can be referred to as “pexophagy.” The disagreement is whether it is correct to use this term when cells are shifted to media lacking nitrogen, as the latter condition is typically used to induce nonspecific autophagy.²¹ Certainly peroxisomes can be degraded nonspecifically; however, when yeast are shifted from oleic acid to media lacking nitrogen, the kinetics and magnitude of degradation suggest a specific process.²² Nonetheless, we may agree that the specific degradation of peroxisomes can be referred to as “pexophagy.” Furthermore, the term “pexophagosome” was proposed to distinguish the sequestering vesicle from the nonspecific autophagosome.¹⁹ Currently, pexophagy has been studied most extensively in yeasts; however, it appears that specific peroxisome degradation occurs in higher eukaryotes as well.^{23,24} Therefore, we propose that the term “pexophagy” be adopted in other systems as research in this area continues.

Similar to the situation with “pexophagy,” there is little reason to disagree about the use of the term “mitophagy”²⁵ (“mitos” is the Greek word for thread). Mitochondria can certainly be sequestered within autophagosomes during nonspecific autophagy, but the term mitophagy refers to specific degradation. The interesting feature of this term is that it has been widely accepted even though there has been relatively little evidence for the occurrence of selective

mitochondrial degradation. The first papers, to our knowledge, providing evidence of selective mitochondrial degradation in a higher eukaryote appeared in 2001;^{26,27} however, more recent papers utilizing yeast have confirmed that mitochondria can be degraded through a specific process.^{28–31} Some data suggest that specific degradation occurs through a microautophagic process involving direct uptake at the vacuole membrane.²⁹ We suggest that this be referred to as “micromitophagy,” whereas engulfment via a double membrane vesicle would be “macromitophagy.”

Unfortunately, this is where the clear consensus ends even though additional terms have been put forth. Among these, one quite useful term is “xenophagy”³² (which is derived from the Greek “xenos” meaning foreign). Thus, “xenophagy” refers to the specific elimination of foreign microbes that are inside a cell, through an autophagy-related process. One criticism of this term is that it was previously used to refer to the accidental swallowing of foreign dental matter (instruments or materials);³³ however, the latter denotation was introduced over a quarter of a century ago and does not seem to have received widespread acceptance or usage. Accordingly, we suggest that this term be used in the autophagy field. Note that “xenophagy” should not be confused with the term “heterophagy,” which derives from the Greek “heteros” meaning different; heterophagy was coined as a term to describe the opposite of autophagy, that is, lysosomal degradation of material not derived from self, but the term heterophagy is used to describe processes involving uptake of exogenous material by invagination of the plasma membrane, such as endocytosis and phagocytosis.

Although the reintroduction of the term “xenophagy” described work relating to bacterial degradation,²³ “xenophagy” has also been used in reference to viruses.³⁴ The term “virophagy” has been used in some meetings to specifically indicate the elimination of viruses through autophagy, although we are not aware of its having appeared in print in this regard; however, there are two reasons that “virophagy” is a less desirable term. First, “xenophagy” is more general and includes not only bacteria and viruses, but also fungi and parasites. Second, a recent paper uses the term “virophagy” to describe the inactivation of viruses by *Tetrahymena* that occurs in sewage water (need we say more?).³⁵ Therefore, we propose that the autophagy community use the term “xenophagy” as it was intended—to include the autophagic removal of any foreign microbes.

Another recently introduced term (appearing in the previous issue of this journal—you cannot get much more recent than that) is “aggrephagy”³⁶ (from the Latin “aggregare” meaning “add to”). This name describes the selective sequestration of protein aggregates via autophagy. Increasing evidence supports the selective enclosure of aggregates within a membrane compartment in a process that is dependent upon Atg proteins.³⁷ Considering the potential medical implications, it is probably worth adopting a separate name; however, we would note that the cytoprotective autophagic removal of brain cell protein aggregates may be due mainly to nonspecific macroautophagy rather than aggrephagy.^{38,39}

Finally we come to one last recently published term, “ER-phagy,”⁴⁰ referring to the selective autophagic sequestration of endoplasmic reticulum membranes, which was actually the first selective autophagic process to be proposed.⁴¹ We are not in favor of this name because it is linguistically rather awkward. Perhaps a more manageable term would be “reticulophagy” (derived from the Latin “reticulatus” for “having a net-like pattern”). Similarly, if there is specific autophagic degradation of the Golgi it seems reasonable to use “golgiphagy,” which is clear in meaning and as a bonus has a certain alliterative

appeal. The degradation of the entire nucleus was shown to occur through a macroautophagic process,⁴² but the authors did not attempt to determine whether this was a specific process, and did not suggest a specific name. If it is specific, an obvious choice would be “nucleophagy.” Finally, what happens if someone shows that lysosomes (or yeast vacuoles) can be selectively sequestered by autophagy? “Lysophagy” would seem to be a suitable name. Although once proposed, in an East German journal,⁴³ as a more appropriate substitute for “microautophagy,” this term did not receive widespread acceptance, and can thus, with the consent of the original lead author, safely be accorded a new connotation. Alternatively, we can use the longer term “lysosomophagy”⁴⁴ that has already appeared in the literature.

SUGGESTED DEFINITIONS

Aggrephagy—the selective autophagic sequestration of protein aggregates.

Autophagy—any process involving degradative delivery of a portion of the cytoplasm to the lysosome or vacuole that does not involve direct transport through the endocytic or vacuolar protein sorting, Vps, pathways.

Chaperone-mediated autophagy (CMA)—import and degradation of soluble cytosolic proteins by chaperone-dependent, direct translocation across the lysosomal membrane.

Crinophagy—the direct fusion of secretory vesicles with lysosomes.

Cytoplasm to vacuole targeting (Cvt)—a biosynthetic pathway in yeast that transports resident hydrolases to the vacuole (the yeast lysosome) through a selective autophagy-related process.

Macroautophagy—the largely nonspecific autophagic sequestration of cytoplasm into a double- or multiple-membrane-delimited compartment (an autophagosome) of nonlysosomal/vacuolar origin. Note that certain proteins may be selectively degraded via macroautophagy, and, conversely, some cytosolic components such as cytoskeletal elements are selectively excluded.

Microautophagy—uptake and degradation of cytoplasm by invagination of the lysosomal/vacuolar membrane.

Mitophagy—the selective autophagic sequestration and degradation of mitochondria.

Pexophagy—a selective type of autophagy involving the sequestration and degradation of peroxisomes; can occur by a micro- or macropexophagic process.

Piecemeal microautophagy of the nucleus—intrusion of portions of the nucleus into the vacuole, followed by scission and degradation.

Reticulophagy—the selective autophagic sequestration and degradation of endoplasmic reticulum.

Vacuole import and degradation—the selective uptake of cytosolic fructose-1,6-bisphosphatase, and possibly other proteins, within 30 nm single membrane vesicles, followed by fusion with the vacuole and degradation.

Xenophagy—the selective degradation of microbes (e.g., bacteria, fungi, parasites and/or viruses) through an autophagy-related mechanism.

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